

**Remarks**

**Rejection of claims 1-11 under 35 USC § 103(a) as being unpatentable over Harada et al. (EP 0 882 719 [Harada et al '719] and Harada et al. (WO 98/57938)[Harada et al. '938]**

Claims 1-11 stand rejected under 35 USC § 103(a) as being unpatentable over Harada et al. '719 and Harada et al. '938. Reconsideration and withdrawal of the rejection is requested in view of the amendment to Claims 1 and 10 and claims dependent therefrom and following remarks.

The Examiner asserts on page 2-4 of the Office Action that the Applicants' claimed subject matter would have been obvious as the cited references teach that the compounds are effective for treating endothelin mediated disorders and the selection of a specific host in which to practice such treatment would have been a matter well within the purview of the skilled artisan.

Claims 1 and 10 have now been amended with specific language that characterizes longer duration of action "such that the free blood plasma concentration after twenty four hours remains above the concentration providing efficacy for said endothelin-mediated disorder," This clearly distinguishes over the two applied references, in that they provide no teaching relating to such unexpected activity relating to free blood plasma concentration. Support for such claim language is found at page 4 lines 21-22.

Specific support of such activity is shown in the pharmacokinetic studies on pages 5 through 9 of the application, where representative compounds X and Y, as disclosed in the specification, were evaluated by comparison to two compounds, including Example 2 of Harada '938. As shown in the table at the bottom of page 8, only compounds X and Y would still be efficacious after 24 hours following a 2.0 mg/kg i.v dose, as they would be present at 100% of the  $K_b$  value or more.

There is no disclosure or suggestion in Harada et al '719 or Harada et al '938, that compounds of formula I, as defined by the Applicants, would possess the aforementioned advantages.

As previously noted in the earlier response, it is the Examiners' duty to explain the specific understanding or principle within the knowledge of the skilled artisan that would motivate one with no knowledge of the Applicants' invention to select the

compounds of formula I, as defined by the Applicants, to provide treatment to companion animals, the treatment having the advantages described in the specification.

"A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art." If the Examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Rijckaert, 9 F.3d 1531, 28 USPQ2d 1955,1956(Fed. Cir. 1993)

Accordingly, it is submitted that the Examiner has not set forth a prima facie case of obviousness under 35 USC § 103. Reconsideration and withdrawal of the rejection of claims 1-11 under 35 USC § 103(a) as being unpatentable over Harada et al '719 and Harada et al. '938 is respectfully requested.

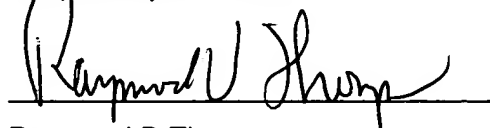
Claims 1 and 10 at lines 9 and 11 following the structure were also amended to remove a pair of improperly placed bracket symbols, delineating a set of optional substituents in the expression for Ar. Those bracket symbols were replaced by simple parenthesis in order to help in claim clarity. Removal of the brackets without substitution of the parenthesis rendered the claim more difficult to interpret. There is no new matter issue raised since these brackets around the expression were present in the specification recitation of that structure and have been removed for formal requirements of proper claim drafting.

Due to the change of certain claim amendment formats under the Waiver of a-d of 37CFR 1.121 contained in a Web notice dated 13Feb2003, no marked-up version of the changes made to claims by current amendment is included with this amendment. Undersigned believes these changes were effective July 1, 2003 and has acted on this understanding in preparation. Early allowance of the claims is respectfully requested.

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Respectfully submitted,



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